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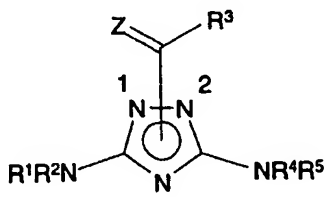
(54) Title: DIAMINO-1,2,4-TRIAZOLE-CARBOXYLIC AND DERIVATIVES AS GSK-3 INHIBITORS




(I)

(57) Abstract: Pharmaceutical compositions comprising compounds of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier wherein; the $R^3CZ$-moiety may be attached to the nitrogen atom at position 1 or the nitrogen atom at position 2; $R^1$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic; $R^2$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic, or $R^1$ and $R^2$ together with the nitrogen atom to which they are attached may form a heterocyclic ring which ring may be unsubstituted or substituted; $R^3$ is alkyl, aryl, aralkyl, aryl(Q)alkyl, where Q is O or S, aralkenyl, alicyclic, heteroaryl, heteroaralkyl, arylcarbonylalkyl, alicyclylalkyl, diarylalkyl, or $NR^6R^7$; $R^4$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic; $R^5$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic, or $R^4$ and $R^5$ together with the nitrogen atom to which they are attached may form a heterocyclic ring which ring may be unsubstituted or substituted; $R^6$ is hydrogen, aryl or alicyclic; $R^7$ is hydrogen, aryl or alicyclic, and: Z is oxygen or sulphur; are indicated to be useful in the treatment of conditions associated with a need for inhibition of GSK-3.

WO 01/09106 A1

# DIAMINO-1,2,4-TRIAZOLE-CARBOXYLIC AND DERIVATIVES AS GSK-3 INHIBITORS

This invention relates to novel compositions, especially pharmaceutical compositions, processes for the preparation of compounds, the use of these compounds in medicine, and to certain novel compounds.

GSK-3 is a serine/threonine protein kinase having a 47kDa monomeric structure. It is one of several protein kinases which phosphorylates glycogen synthase (GS) (Embi *et al.* Eur. J. Biochem. (107) 519-527 (1980)). Two isoforms are found in mammalian cells: α and β. Both isoforms phosphorylate muscle glycogen synthase (Cross *et al.* Biochemical Journal (303) 21-26 (1994)) and these two isoforms show good homology between species (e.g. human and rabbit GSK-3α are 96% identical).

Type 2 diabetes (or Non-Insulin Dependent Diabetes Mellitus, NIDDM) is a multifactorial disease. Hyperglycaemia is due to insulin resistance in the liver, muscle and other tissues coupled with inadequate or defective secretion of insulin from pancreatic islets. Skeletal muscle is the major site for insulin-stimulated glucose uptake and in this tissue, glucose removed from the circulation is either metabolised through glycolysis and the TCA cycle, or stored as glycogen. Muscle glycogen deposition plays the more important role in glucose homeostasis and Type 2 diabetic subjects have defective muscle glycogen storage.

The stimulation of glycogen synthesis by insulin in skeletal muscle results from the dephosphorylation and activation of glycogen synthase (Villar-Palasi C. and Larner J. Biochim. Biophys. Acta (39) 171-173 (1960), Parker P. J. *et al.* Eur. J. Biochem. (130) 227-234 (1983), and Cohen P. Biochem. Soc. Trans. (21) 555-567 (1993)). The phosphorylation and dephosphorylation of GS are mediated by specific kinases and phosphatases. GSK-3 is responsible for phosphorylation and deactivation of GS, while glycogen bound protein phosphatase 1 (PP1G) dephosphorylates and activates GS. Insulin both inactivates GSK-3 and activates PP1G (Srivastava A. K. and Pandey S. K. Mol. and Cellular Biochem. (182) 135-141 (1998).

Chen *et al.* Diabetes (43) 1234-1241 (1994) found that there was no difference in the mRNA abundance of PP1G between patients with Type 2 diabetes and control patients, suggesting that an increase in GSK-3 activity might be important in Type 2 diabetes. It has also recently been demonstrated that GSK-3 is overexpressed in Type 2 diabetic muscle and that an inverse correlation exists between skeletal muscle GSK-3α activity and insulin action (Nikoulina *et al.* Glycogen Synthase Kinase-3 in Human Skeletal Muscle: Relationship To Insulin Resistance in Type 2 Diabetes Diabetes (47(1)) 0028 Page A7 (1998) (Oral presentation)). Additionally, in CHO cells, expressing both insulin receptor and insulin receptor substrate 1 (IRS-1), overexpression of GSK-3 resulted in an

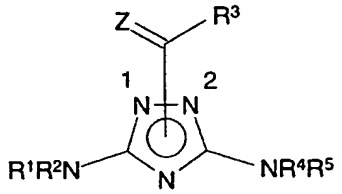
impairment of insulin action (Eldar-Finkelman and Krebs PNAS (94) 9660-9664 (1997)).

GSK-3 has been shown to phosphorylate other proteins in vitro, e.g. tau protein, which is hyperphosphorylated in Alzheimer's disease, and the eukaryotic initiation factor eIF-2B at $Serine^{540}$. GSK-3 is known to be inhibited by lithium (Stambolic V., Ruel L.and Woodgett J.R. Curr. Biol. 1996 6(12): 1664-8) and lithium reduces the phosphorylation of tau, enhances the binding of tau to microtubules, and promotes microtubule assembly through direct and reversible inhibition of glycogen synthase kinase-3 (Hong M., Chen D.C., Klein P.S. and Lee V.M. J.Biol. Chem. 1997 272(40) 25326-32). International Application Publication Number WO 97/41854 (University of Pennsylvania) discloses that an effective drug for the treatment of manic depression is lithium, but that there are serious drawbacks associated with this treatment and the molecular mechanism underlying the action of lithium in the treatment of manic depression has not been elucidated.

United States patent 2,456,090 (Libbey-Owens-Ford Glass Company) discloses 3,5-diamino-2-benzoyl-1,2,4-triazole as a precursor in the production of synthetic resins. Blank B. *et al.* J. Med. Chem. 15(6) 694 (1972) discloses certain 1,2,4-triazoles as potential hypoglycaemic agents. Certain 1,2,4-triazoles are also known from the Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall, PL34 0HW, UK.

It has now surprisingly been found that particular triazole compounds, including a series of novel compounds, are particularly potent and selective inhibitors of GSK-3. These compounds are therefore indicated to be useful for the treatment of conditions associated with a need for the inhibition of GSK-3 such as diabetes, especially Type 2 diabetes, dementias, such as Alzheimer's disease, and manic depression.

Accordingly, the present invention provides a pharmaceutical composition, which composition comprises a compound of formula (I)




(I)

or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier wherein;

the $R^3CZ$- moiety may be attached to the nitrogen atom at position 1 or the nitrogen atom at position 2;

$R^1$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic;

$R^2$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic, or $R^1$ and $R^2$ together with the nitrogen atom to which they are attached may form a heterocyclic ring which ring may be unsubstituted or substituted;

$R^3$ is alkyl, aryl, aralkyl, aryl(Q)alkyl, where Q is O or S, aralkenyl, alicyclic, heteroaryl, heteroaralkyl, arylcarbonylalkyl, alicyclylalkyl, diarylalkyl, or $NR^6R^7$;

$R^4$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic;

$R^5$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic, or $R^4$ and $R^5$ together with the nitrogen atom to which they are attached may form a heterocyclic ring which ring may be unsubstituted or substituted;

$R^6$ is hydrogen, aryl or alicyclic;

$R^7$ is hydrogen, aryl or alicyclic, and;

Z is oxygen or sulphur.

Suitably, $R^1$ is hydrogen or unsubstituted or substituted phenyl, wherein the substituents for the phenyl group are independently selected from up to three of $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkoxy $C_1$-$C_6$alkyl, aryl, aryloxy, halo, hydroxy, carboxy, cyano, and nitro.

Favourably, $R^1$ is phenyl either unsubstituted or substituted with up to three of methyl, methoxy, or chloro.

Suitably, $R^2$ is hydrogen or unsubstituted or substituted phenyl, wherein the substituents for the phenyl group are independently selected from up to three of $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkoxy $C_1$-$C_6$alkyl, aryl, aryloxy, halo, hydroxy, carboxy, cyano, and nitro.

Favourably, $R^2$ is hydrogen.

Suitably, $R^3$ is unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl, unsubstituted or substituted benzyl, unsubstituted or substituted thienylmethyl, unsubstituted or substituted phenylthiomethyl, unsubstituted or substituted naphthylmethyl, unsubstituted or substituted furylethenyl, unsubstituted or substituted cyclohexyl, unsubstituted or substituted pyridyl, unsubstituted or substituted indolylmethyl, unsubstituted or substituted phenylcarbonylethyl, unsubstituted or substituted cyclopentenylmethyl, unsubstituted or substituted phenylpropyl, unsubstituted or substituted diphenylethyl, wherein the substituents for the $R^3$ aryl groups are selected from -$O(CH_2)_nO$-, where n is 1 to 3, or up to three of halo, aryl, perfluoro$C_1$-$C_6$alkyl, nitro, arylcarbonyl, aryloxy, $C_1$-$C_6$acyl;

or $R^3$ is $NR^6R^7$ where $R^6$ and $R^7$ are each independently hydrogen, unsubstituted or substituted aryl, or unsubstituted or substituted $C_1$-$C_6$alicyclic, wherein the

substituents for the $R^6$ and $R^7$ groups are independently selected from up to three of halo, aryl, aryloxy, alkyl, nitro, and alkoxy.

Favourably, $R^3$ is phenyl either unsubstituted or substituted with up to three of chloro, bromo, phenyl, trifluoromethyl, nitro, benzoyl, phenoxy, acetyl, or 3,4-$OCH_2O$-; naphthyl; benzyl either unsubstituted or substituted with up to three of phenyl or fluoro; 2-thienylmethyl; phenylthiomethyl 2-naphthylmethyl; cyclohexyl; 3-pyridyl; 3-indolylmethyl; phenylcarbonylethyl; cyclopent-2-enylmethyl; phenylpropyl; 2,2-diphenylethyl; or 2-furylethenyl; or $NR^6R^7$ where $R^6$ and $R^7$ are each independently hydrogen, phenyl either unsubstituted or substituted with up to three of chloro, phenyl, phenoxy, methyl, bromo, nitro, or methoxy; cyclohexyl; or 1-naphthyl.

Suitably, $R^4$ is hydrogen.

Suitably, $R^5$ is hydrogen.

Suitably, $R^6$ is unsubstituted or substituted aryl or unsubstituted or substituted alicyclic.

Favourably $R^6$ is cyclohexyl, naphthyl or phenyl which phenyl group may be either unsubstituted or substituted with up to three of chloro, bromo, phenyl, methyl, phenoxy, nitro or methoxy.

Suitably, $R^7$ is hydrogen.

In a particular aspect, the pharmaceutical composition provided by the invention comprises a compound of formula (I) selected from the list consisting of:

3-amino-5-anilino-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-*trans*-(2-furyl)acryloyl)1,2,4,-triazole;
3-amino-5-anilino-1-(3-*trans*-(2-furyl)acryloyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide;
3-amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide;
3-amino-5-(5-chloro-2-methylanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-(4-chlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-naphthoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-phenylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-trifluoromethylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-((3-benzoyl)benzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-biphenylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-thienylacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-phenylthioacetyl-1,2,4-triazole;

3-amino-5-(3-chloroanilino)-2-(2-naphthylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-phenoxybenzoyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-cyclohexylcarbonyl-1,2,4-triazole;
3-amino-5-anilino-2-phenylacetyl-1,2,4-triazole;
3-amino-5-anilino-2-(3-nicotinoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3,5-dichlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-acetylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-indolylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-fluorophenylacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3-benzoylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(cyclopent-2-enyl)acetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(4-phenylbutyroyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3,3-diphenylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid 4-biphenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-phenoxyphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-bromo-2-methylphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (1-naphthyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-nitrophenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-methoxyphenyl)amide;
3,5-diamino-2-benzoyl-1,2,4-triazole, and;
3-amino-5-(4-methoxyanilino)-1,2,4-triazole-2-carboxylic acid (4-chlorophenyl)amide;
or a pharmaceutically acceptable derivative thereof.

There is a sub-group of compounds, falling wholly within formula (I) and being of formula (IA), wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, and Z are as defined in relation to formula (I), with the proviso that the compounds of formula (IA) do not include:
3,5-diamino-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-acetyl-1,2,4-triazole, and;
3-amino-5-(4-methoxyanilino)-1,2,4-triazole-2-carboxylic acid (4-chlorophenyl)amide.

Compounds of formula (IA) and derivatives thereof are considered to be novel and accordingly form a further aspect of the invention. Examples of compounds of formula (IA) include:
3-amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-*trans*-(2-furyl)acryloyl)-1,2,4,-triazole;

3-amino-5-anilino-1-(3-*trans*-(2-furyl)acryloyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide;
3-amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide;
3-amino-5-(5-chloro-2-methylanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-(4-chlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-naphthoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-phenylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-trifluoromethylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-((3-benzoyl)benzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-biphenylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-thienylacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-phenylthioacetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(2-naphthylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-phenoxybenzoyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-cyclohexylcarbonyl-1,2,4-triazole;
3-amino-5-anilino-2-phenylacetyl-1,2,4-triazole;
3-amino-5-anilino-2-(3-nicotinoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3,5-dichlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-acetylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-indolylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-fluorophentlacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3-benzoylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(cyclopent-2-enyl)acetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(4-phenylbutyroyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3,3-diphenylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid 4-biphenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-phenoxyphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-bromo-2-methylphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (1-naphthyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-nitrophenyl)amide, and;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-methoxyphenyl)amide.

There is a sub-group of compounds, falling wholly within formula (I) and being of formula (IB), wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, and Z are as defined in relation

to formula (I), with the proviso that the compounds of formula (IB) do not include:
3,5-diamino-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-benzoyl-1,2,4-triazole, and;
3-amino-5-(4-methoxyanilino)-1,2,4-triazole-2-carboxylic acid (4-chlorophenyl)amide.

Compounds of formula (IB) and derivatives thereof are considered to be novel and accordingly form a further aspect of the invention. Examples of compounds of formula (IB) include:
3-amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-*trans*-(2-furyl)acryloyl)-1,2,4,-triazole;
3-amino-5-anilino-1-(3-*trans*-(2-furyl)acryloyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide;
3-amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide;
3-amino-5-(5-chloro-2-methylanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-(4-chlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-naphthoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-phenylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-trifluoromethylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-((3-benzoyl)benzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-biphenylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-thienylacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-phenylthioacetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(2-naphthylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-phenoxybenzoyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-cyclohexylcarbonyl-1,2,4-triazole;
3-amino-5-anilino-2-phenylacetyl-1,2,4-triazole;
3-amino-5-anilino-2-(3-nicotinoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3,5-dichlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-acetylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-indolylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-fluorophenylacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3-benzoylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(cyclopent-2-enyl)acetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(4-phenylbutyroyl)-1,2,4-triazole;

3-amino-5-(3-chloroanilino)-2-(3,3-diphenylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid 4-biphenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-phenoxyphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-bromo-2-methylphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (1-naphthyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-nitrophenyl)amide, and;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-methoxyphenyl)amide.

Certain of the compounds of formulae (IA) and (IB) may exist in one or more stereoisomeric forms, including geometric isomers. The present invention encompasses all of the isomeric forms of the compounds of formulae (IA) and (IB), including geometric isomers, whether as individual isomers or as mixtures of isomers, including racemates.

Alkyl groups referred to herein, including those forming part of other groups, include straight or branched chain alkyl groups containing up to six carbon atoms, said carbon atoms being optionally substituted with up to five, suitably up to three, groups selected from the list consisting of carboxy and esters and amides thereof, hydroxamic acids and esters thereof, hydroxy, halogen, amino, alkylamino, and dialkylamino.

Alkenyl groups referred to herein include straight and branched chain alkenyl groups containing from two to six carbon atoms, said carbon atoms being optionally substituted with up to five, suitably up to three, groups including those substituents described hereinbefore for the alkyl group.

Alicyclic groups referred to herein include cycloalkyl and cycloalkenyl groups having between three and eight ring carbon atoms, which carbon atoms are optionally substituted with up to five, suitably up to three, groups including those substituents described hereinbefore for the alkyl group.

The term "aryl" when used herein includes phenyl and naphthyl, especially phenyl.

Suitable optional substituents for any aryl group include up to three substituents selected from the list consisting of halo, alkyl, alkenyl, substituted alkenyl, arylalkyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkyloxy, hydroxy, hydroxyalkyl, nitro, amino, cyano, cyanoalkyl , mono- and di-N-alkylamino, acyl, acylamino, N-alkylacylamino, acyloxy, carboxy, carboxyalkyl, carboxyalkylcarbonyl, carboxyalkenyl, ketoalkylester, carbamoyl, carbamoylalkyl, mono- and di-N-alkylcarbamoyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy, arylthio, aralkyloxy, aryloxycarbonyl, ureido, guanidino, morpholino, adamantyl, oxazolyl, aminosulphonyl, alkylaminosulphonyl, alkylthio, haloalkylthio, alkylsulphinyl, alkylsulphonyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, trityl, substituted trityl, mono- or bis-

Suitable pharmaceutically acceptable acid addition salts provided by pharmaceutically acceptable inorganic acids includes the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and hydroiodide.

Suitable pharmaceutically acceptable acid addition salts provided by pharmaceutically acceptable organic acids includes the acetate, tartrate, maleate, fumarate, malonate, citrate, succinate, lactate, oxalate, benzoate, ascorbate, methanesulphonate, alpha-keto glutarate and alpha-glycerophosphate.

Suitable pharmaceutically acceptable solvates include hydrates.

For the avoidance of doubt when used herein the term "treatment of diabetes " includes treatment of diabetes mellitus, especially Type 2 diabetes, and conditions associated with diabetes mellitus.

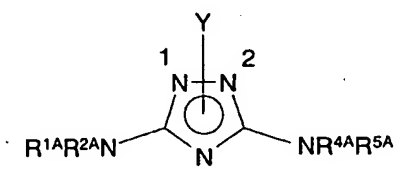
The term 'conditions associated with diabetes' includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

The term 'conditions associated with the pre-diabetic state' includes conditions such as insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

The term 'conditions associated with diabetes mellitus itself' include hyperglycaemia, insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance.

The term 'complications associated with diabetes mellitus' includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy. Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

A further aspect of the invention provides a process for the preparation of a compound of formula (I), wherein Z is O and $R^3$ is other than $NR^6R^7$, or a derivative thereof, which process comprises the reaction of a compound of formula (II)




(II)

wherein Y is hydrogen and $R^{1A}$, $R^{2A}$, $R^{4A}$ and $R^{5A}$ are respectively $R^1$, $R^2$, $R^4$ and $R^5$ as hereinbefore defined or a protected form thereof, with a compound of formula (III)

$R^{3A}X$

(III)

wherein $R^{3A}$ is alkyl, aryl, aralkyl, aryl(Q)alkyl, where Q is O or S, aralkenyl, alicyclic, heteroaryl, heteroaralkyl, arylcarbonylalkyl, alicyclylalkyl, diarylalkyl, or a protected form thereof, and X is a suitable acylating group such as –COL, wherein L is a hydroxy group which has been activated by esterification with, for example, 1-hydroxybenzotriazole, or L is a suitable leaving group such as chloro, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I), wherein Z is O and $R^3$ is other than $NR^6R^7$, to a further compound of formula (I), wherein Z is O and $R^3$ is other than $NR^6R^7$;

(ii) removing any necessary protecting group;

(iii) preparing a derivative of the compound so formed.

Suitably, Y is at position 1 or position 2.

The reaction between the compounds of formulae (II) and (III) may be carried out in any suitable solvent, for example dimethyl formamide, under suitable acylation conditions, for example using an active ester of a carboxylic acid in the presence of a peptide coupling agent, at any temperature providing a suitable rate of formation of the required product, generally ambient temperature, over a suitable reaction time, generally 24 hours.

Suitable reaction temperatures include those in the range of 0-30°C. Conventional methods of heating and cooling such as thermostatically controlled electric heating mantles and ice baths may be employed.

The reaction products are isolated using conventional methods. Typically, water is added and the resultant solid product removed by filtration. The reaction products are purified by conventional methods, such as chromatography, recrystallisation, and trituration.

Preferably, X is –COL, wherein L is a hydroxy group which has been activated by esterification with 1-hydroxybenzotriazole.

In a preferred aspect, a mixture of a compound of formula (II), a compound of formula (III) wherein L is hydroxy, 1-hydroxybenzotriazole, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in dry dimethylformamide, wherein the carbodiimide is added last, is stirred at ambient

temperature for about 24 hours. Water is then added and the resulting solid product is isolated by filtration, washed with water and dried *in vacuo*.

A further aspect of the invention provides a process for the preparation of a compound of formula (I), wherein Z is O and $R^3$ is $NHR^6$, or a derivative thereof, which process comprises the reaction of a compound of formula (II) as hereinbefore defined with a compound of formula (IV)

$R^{6A}T$

(IV)

wherein $R^{6A}$ is $R^6$ as hereinbefore defined, or a protected form thereof, and T is a suitable aminocarbonylating group such as isocyanate, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I), wherein Z is O and $R^3$ is $NHR^6$, to a further compound of formula (I), wherein Z is O and $R^3$ is $NHR^6$;

(ii) removing any necessary protecting group;

(iii) preparing a derivative of the compound so formed.

Suitably, Y is at position 1 or position 2.

The reaction between the compounds of formulae (II) and (IV) may be carried out in any suitable solvent, for example dimethyl formamide, under conventional aminocarbonylating conditions at any temperature providing a suitable rate of formation of the required product, generally ambient temperature, over a suitable reaction time, generally 48 hours.

Suitable reaction temperatures include those in the range of 20-30°C. Conventional methods of heating and cooling such as thermostatically controlled electric heating mantles and ice baths may be employed.

The reaction products are isolated using conventional methods. Typically, water is added and the resultant solid product removed by filtration. The reaction products are purified by conventional methods, such as chromatography, recrystallisation, and trituration.

Preferably T is isocyanate.

In a preferred aspect, a mixture of the isocyanate of formula (IV) and the compound of formula (II) in dry dimethyl formamide is stirred for about 48 hours and water added. The resulting solid product is isolated by filtration, washed with water and dried *in vacuo*.

A further aspect of the invention provides a process for the preparation of a compound of formula (I), wherein Z is S and $R^3$ is other than $NR^6R^7$, or a derivative thereof, which process comprises the reaction of a compound of formula (II) as hereinbefore defined with a compound of formula (V)

$R^{3A}W$

(V)

wherein $R^{3A}$ is alkyl, aryl, aralkyl, aryl(Q)alkyl, where Q is O or S, aralkenyl, alicyclic, heteroaryl, heteroaralkyl, arylcarbonylalkyl, alicyclylalkyl, diarylalkyl, or a protected form thereof, and W is a suitable thioacylating group such as –CSM, wherein M is a suitable leaving group such as chloro, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I), wherein Z is S and $R^3$ is other than $NR^6R^7$, to a further compound of formula (I), wherein Z is S and $R^3$ is other than $NR^6R^7$;

(ii) removing any necessary protecting group;

(iii) preparing a derivative of the compound so formed.

Suitably, Y is at position 1 or position 2.

The reaction between the compounds of formulae (II) and (V) may be carried out using procedures similar to those described in Walter W and Radke M Justus Liebigs Ann. Chem. 636 (1973).

A further aspect of the invention provides a process for the preparation of a compound of formula (I), wherein Z is S and $R^3$ is $NHR^6$, or a derivative thereof, which process comprises the reaction of a compound of formula (II) as hereinbefore defined with a compound of formula (VI)

$R^{6A}U$

(VI)

wherein $R^{6A}$ is $R^6$ as hereinbefore defined, or a protected form thereof, and U is a suitable aminothiocarbonylating group such as isothiocyanate, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I), wherein Z is S and $R^3$ is $NHR^6$, to a further compound of formula (I), wherein Z is S and $R^3$ is $NHR^6$;

(ii) removing any necessary protecting group;

(iii) preparing a derivative of the compound so formed.

Suitably, Y is at position 1 or position 2.

The reaction between the compounds of formulae (II) and (VI) may be carried out using procedures similar to those described in Reiter J *et al* J. Heterocycl. Chem. 24(6) 1685-1695 (1987).

The above mentioned conversions of a compound of formula (I) into another compound formula (I) includes any conversion which may be effected using conventional procedures.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

Where appropriate individual isomeric forms of the compounds of formula (I) may be prepared as individual isomers using conventional chemical procedures.

The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

The derivatives of the compounds of formula (I), including salts and/or solvates, may be prepared and isolated according to conventional procedures.

Compounds of formula (II) are known and may be prepared using methods analogous to those used to prepare such compounds such as those described in Blank B. *et al.* J. Med. Chem. 15(6) 694 (1972). The compounds of formula (II) may be interconverted in an analogous manner to the above mentioned inter-conversions of the compounds of formula (I).

The compounds of formula (III) are known, commercially available compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in standard reference texts of synthetic methodology such as March J. Advanced Organic Chemistry 3rd Edition (1985) Wiley Interscience.

Amidotriazoles wherein the amido nitrogen atom is disubstituted are known for example in Banks. R *et al.* J. Chem. Soc. Perkin Trans. 1 (19) 1836-1840 (1975).

As stated above, the compounds of formula (I), or derivatives thereof, are indicated to be useful as inhibitors of GSK-3.

Accordingly, in a further aspect, the present invention provides a compound of formula (I), or a derivative thereof, for use in the treatment of conditions associated with the need for the inhibition of GSK-3 such as diabetes, especially Type 2 diabetes, dementias such as Alzheimer's disease and manic depression.

In still a further aspect, the present invention provides the use of a compound of formula (I), or a derivative thereof, for the manufacture of a medicament for the treatment of conditions associated with the need for the inhibition of GSK-3 such as diabetes, especially Type 2 diabetes, dementias such as Alzheimer's disease and manic depression.

In yet a further aspect, the present invention provides a method for the treatment of conditions associated with the need for the inhibition of GSK-3 such as diabetes, especially Type 2 diabetes, dementias such as Alzheimer's disease and manic depression, which method comprises the administration of a

pharmaceutically effective, non-toxic amount of a compound of formula (I) or a derivative thereof.

The compounds of formula (I), or a derivative thereof, are usually administered as the sole medicament but they may be administered in combination with other medicament agents as dictated by the severity and type of disease being treated. For example in the treatment of diabetes, especially Type 2 diabetes, a compound of formula (I), or a derivative thereof, may be used in combination with other medicament agents, especially antidiabetic agents such as insulin secretagogues, especially sulphonylureas, insulin sensitisers, especially glitazone insulin sensitisers (for example thiazolidinediones), or with biguanides or alpha glucosidase inhibitors or the compound of formula (I), or a derivative thereof, may be administered in combination with insulin.

The said combination comprises co-administration of a compound of formula (I), or a derivative thereof, and an additional medicament agent or the sequential administration of a compound of formula (I), or a derivative thereof, and the additional medicament agent.

Co-administration includes administration of a pharmaceutical composition which contains both a compound of formula (I), or a derivative thereof, and the additional medicament agent or the essentially simultaneous administration of separate pharmaceutical compositions of a compound of formula (I), or a derivative thereof, and the additional medicament agent.

The compositions of the invention are preferably adapted for oral administration. However, they may be adapted for other modes of administration. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions. In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose. Preferably the composition are in unit dosage form. A unit dose will generally contain from 0.1 to 1000 mg of the active compound.

Generally an effective administered amount of a compound of the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be administered once or more times a day for example 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 800 mg/kg/day.

Suitable dose forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example

starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilising the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The formulations mentioned herein are carried out using standard methods such as those described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press), or the above mentioned publications.

Suitable methods for preparing and suitable unit dosages for the additional medicament agent, such as the antidiabetic agent mentioned herein include those methods and dosages described or referred to in the above mentioned reference texts.

**GSK-3 Assays**

Types of GSK-3 assay used to test the compounds of the invention include the following:

**Type 1:** The GSK-3 specific peptide used in this assay was derived from the phosphorylation site of glycogen synthase and its sequence is: YRRAAVPPSPSLSRHSSPHQ(S)EDEEE. (S) is pre-phosphorylated as is glycogen synthase in vivo and the three consensus sites for GSK-3 specific phosphorylation are underlined. The buffer used to make up the glycogen synthase peptide and [$\gamma$-$^{33}$P] ATP consisted of MOPS 25mM, EDTA 0.2mM, magnesium acetate 10mM, Tween-20 0.01% and mercaptoethanol 7.5mM at pH 7.00.

The compounds were dissolved in dimethyl sulphoxide (DMSO) to a final concentration of 100mM. Various concentrations were made up in DMSO and mixed with the substrate (GSK-3 peptide) solution (to a final concentration 20uM) described in the above section along with rabbit or human GSK-3$\alpha$ and GSK-3$\beta$ (final concentration 0.5U/ml enzyme). The reactions were initiated with the addition of [$\gamma$-$^{33}$P] ATP (500cpm/pmole) spiked into a mixture of ATP (final concentration of 10$\mu$M). After 30 min at room temperature the reaction was terminated by the addition of 10$\mu$l of $H_3PO_4$ / 0.01% Tween-20 (2.5%). A volume (10$\mu$l) of the mixture was spotted onto P-30 phosphocellulose paper (Wallac & Berthold, EG&G Instruments Ltd, Milton Keynes). The paper was washed four times in $H_3PO_4$ (0.5%), 2 mins for each wash, air dried and the radioactive phosphate incorporated into the synthetic glycogen synthase peptide, which binds to the P-30 phosphocellulose paper, was counted in a Wallac microbeta scintillation counter.

Analysis of Data: Values for $IC_{50}$ for each inhibitor were calculated by fitting a four-parameter logistic curve to the model : cpm=lower+(upper-lower) /(1 + (concentration/ $IC_{50}$) $^{slope}$).

**Type 2:** This protocol is based on the ability of the kinase to phosphorylate a biotinylated 26 mer peptide, Biot-KYRRAAVPPSPSLSRHSSPHQ(S)EDEEE, the sequence of which is derived from the phosphorylation site of glycogen synthase, where (S) is a pre-phosphorylated serine as in glycogen synthase *in vivo* and the three consensus sites for GSK-3 specific phosphorylation are underlined. The phosphorylated biotinylated peptide is then captured onto Streptavidin coated SPA beads

(Amersham Technology), where the signal from the $^{33}P$ is amplified via the scintillant contained in the beads.

Using microtitre plates, GSK-3 was assayed in 50 mM MOPS buffer, pH 7.0, containing 5% glycerol, 0.01% Tween-20, 7.5 mM 2-mercaptoethanol, 10 mM magnesium acetate, 8 uM of the above peptide, and 10 uM [$^{33}P$]-ATP. After incubation at room temperature, the reaction was stopped by addition of 50 mM EDTA solution containing the Streptavidin coated SPA beads to give a final 0.2 mgs. Following centrifugation, the microtitre plates are counted in a Trilux 1450 microbeta liquid scintillation counter (Wallac). $IC_{50}$ values are generated for each compound by fitting to a four parameter model.

The most potent compounds of the present invention show $IC_{50}$ values in the range of from between 10 to 100 nM.

No adverse toxicological effects are expected for the compounds of the invention, when administered in accordance with the invention.

The following Examples illustrate the invention, but do not limit it in any way:

**Example 1**

**3-Amino-5-anilino-2-benzoyl-1,2,4-triazole**

Benzoyl chloride (0.33 mL, 2.85 mmol) was added dropwise with stirring to an ice-bath cooled solution of 3-amino-5-anilino-1,2,4-triazole (0.5g. 2.85 mmol) in a mixture of acetone (24 mL) and pyridine (0.29 mL). After stirring for 1 hour at bath temperature the mixture was allowed to warm to room temperature and then stirred for a further 8 hours. After storing in a refrigerator at about 4°C for two days, the mixture was poured into water (100 mL) and the resulting solid washed with water and dried *in vacuo*. Recrystallisation from ethanol afforded the title compound as a crystalline solid.

$^1H$ NMR (DMSO-$d_6$): δ6.83 (1H, t), 7.20 (2H, t), 7.45-7.75 (5H, overlapping m), 7.82(2H, br), 8.15 (2H, d) and 9.29 (1H, s).

MS (APCI +ve): $[M+H]^+$ at m/z 280 ($C_{15}H_{13}N_5O$ requires $[M+H]^+$ at m/z 280).

**Example 2**

**3-Amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole**

A mixture of 3-amino-5-anilino-1,2,4-triazole (1.5g, 8.57 mmol), 3,4-methylenedioxybenzoic acid (1.41g, 8.49 mmol), and 1-hydroxybenzotriazole (1.16g, 8.58 mmol) in dry dimethylformamide (45 mL) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.635g, 8.53 mmol), the latter reagent being added last, was stirred at room temperature for 24 hours. Water (90 mL) was added and the resulting solid isolated, washed with water, and dried *in vacuo*. A suspension of the crude product in ethyl acetate (100 mL) was

placed in an ultrasonic bath for 10 minutes. The resulting solid was isolated and dried to give the title compound.

$^1$H NMR (DMSO-$d_6$): δ6.18 (2H, s), 6.84 (1H, t), 7.11 (1H, d), 7.22 (2H, t), 7.52 (2H, d), 7.79 ((3H, br m), 7.90 (1H, dd), and 9.29 (1H, br s).

MS (APCI +ve): $[M+H]^+$ at m/z 324 ($C_{16}H_{13}N_5O_3$ requires $[M+H]^+$ at m/z 324).

**Example 3a**

**3-Amino-5-anilino-2-(3-trans-(2-furyl)acryloyl)-1,2,4-triazole, and**

**Example 3b**

**3-Amino-5-anilino-1-(3-trans-(2-furyl)acryloyl)-1,2,4-triazole**

A mixture of the isomers 3a and 3b was obtained using the general procedure described in Example 2, but using 3-amino-5-anilino-1,2,4-triazole (0.05g, 0.286mmol) and 3-trans-(2-furyl)acrylic acid (0.0395g, 1 equiv.). The individual isomers 3a and 3b were separated by chromatography on silica gel with initially dichloromethane as eluent and then 1:1 ethyl acetate : hexane. The least retained isomer 3b was obtained as a solid from the earlier fractions after evaporation of solvents.

$^1$H NMR (DMSO-$d_6$): δ6.16 (2H, br s), 6.71 (1H, dd), 7.10-7.13 (2H, m, overlapping signals), 7.26-7.43 (3H, m, overlapping signals), 7.62-7.78 (3H, m, overlapping signals), 7.94 (1H, br s), and 10.03 (1H, br s). The signals at δ6.16 and 10.03 exchanged on addition of $D_2O$.

MS (APCI +ve): $[M+H]^+$ at m/z 296 ($C_{15}H_{13}N_5O_2$ requires $[M+H]^+$ at m/z 296).

The most retained isomer 3a was obtained as a solid from the later fractions:

$^1$H NMR (DMSO-$d_6$): δ6.16 (2H, br s), 6.72 (1H, dd), 6.87 (1H, t), 7.11 (1H, d), 7.28 (2H, t), 7.36 (1H, d), 7.58 (2H, d), 7.62-7.80 (3H, overlapping br s and d),7.97 (1H, d), and 9.30(1H, s). The signals at δ7.70 and 9.30 exchanged on addition of $D_2O$ leaving a one proton doublet within the original range δ7.62-7.80 for the former signal.

MS (APCI +ve): $[M+H]^+$ at m/z 296 ($C_{15}H_{13}N_5O_2$ requires $[M+H]^+$ at m/z 296).

**Example 4**

**3-Amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide**

A mixture of 3-amino-5-anilino-1,2,4-triazole (0.1g, 0.57 mmol) and phenyl isocyanate (62 uL, 0.57 mmol) in anhydrous dimethylformamide (2 mL) was stirred at room temperature for 5 days. Water (4 mL) was then added and after stirring for a further 2 hours the resulting solid was collected, washed with water and dried *in vacuo* to afford the title compound.

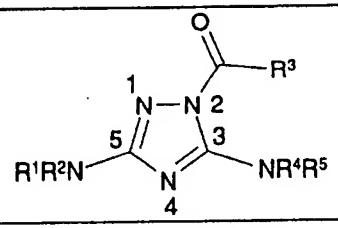
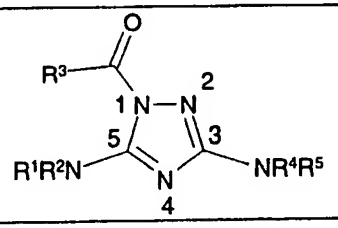
$^1$H NMR (DMSO-$d_6$): δ6.85 (1H, t), 7.10-7.45 (7H, overlapping m), 7.67 (4H, t), 9.18 (1H, s), and 9.52 (1H, s).
MS (APCI +ve): $[M+H]^+$ at m/z 295 ($C_{15}H_{14}N_6O$ requires $[M+H]^+$ at m/z 295).

**Example 5a**
**3-Amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide and,**
**Example 5b**
**3-Amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide**

3-Amino-5-anilino-1,2,4-triazole (0.1g, 0.57 mmol) was reacted with cyclohexyl isocyanate (71mg, 0.57 mmol) using the method described Example 4 except the reaction mixture was shaken rather than being stirred. Water (4 mL) was added and the mixture allowed to stand at room temperature overnight whereupon a solid product was formed. The isomers were separated by chromatography on silica gel with 1:1 ethyl acetate : hexane as eluent. The least retained isomer, 5b, was obtained as a solid from the earlier fractions.
$^1$H NMR (DMSO-$d_6$): δ0.98-1.88 (10H, overlapping m), 3.57 (1H, br m), 5.80 (2H, br s), 7.01 (1H, t), 7.32 (2H, t), 7.44 (1H, d), 7.66 (2H,d) and 9.72 (1H, s). The signals at δ5.80, 7.44 and 9.72 exchanged with $D_2O$.
MS (ES +ve): $[M+H]^+$ at m/z 301 ($C_{15}H_{14}N_6O$ requires $[M+H]^+$ at m/z 301).
The most retained isomer, 5a, was obtained from the later fractions.
$^1$H NMR (DMSO-$d_6$): δ0.98-1.90 (10H, overlapping m), 3.58 (1H, br m), 6.83 (1H, t), 7.22 (4H, m), 7.33 (1H, d), 7.58 (2H, d) and 9.07 (1H, s). The signals at δ7.33 and 9.07 exchanged with $D_2O$.
MS (ES +ve): $[M+H]^+$ at m/z 301 ($C_{15}H_{14}N_6O$ requires $[M+H]^+$ at m/z 301).

The further Examples described in Table 1 herein were prepared according to the methods herein described or by analogy thereto, with particular reference to Examples 1 to 5b above. Examples 1 to 5b above are themselves included in Table 1 as Examples 1 to 5b.

## Table 1

|  |  |
|---|---|
| **Structure Type A** | **Structure Type B** |

| Example No. | Structure Type | R1 | R2 | R3 | R4 | R5 | MS (APcI +ve) $[M+H]^+$ (observed) | For Procedure see Example No. |
|---|---|---|---|---|---|---|---|---|
| 1 | A | Ph | H | Ph | H | H | 280 | 1 |
| 2 | A | Ph | H | 3,4-(-OCH2O-)Ph | H | H | 324 | 2 |
| 3a | A | Ph | H | trans-(2-Furyl)ethenyl | H | H | 296 | 3 |
| 3b | B | Ph | H | trans-(2-Furyl)ethenyl | H | H | 296 | 3 |
| 4 | A | Ph | H | PhNH | H | H | 295 | 4 |
| 5a | A | Ph | H | CyclohexylNH | H | H | 301[a] | 5 |
| 5b | B | Ph | H | CyclohexylNH | H | H | 301[a] | 5 |
| 6 | A | 5-Cl-2-MePh | H | Ph | H | H | 328/330 | 2 |
| 7 | A | Ph | H | 4-ClPh | H | H | 314/316 | 2 |
| 8 | A | Ph | H | 2-Naphthyl | H | H | 330 | 2 |

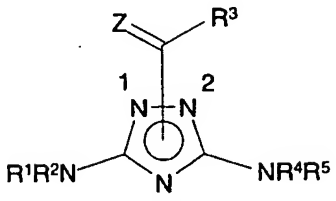
| Example No. | Structure Type | R1 | R2 | R3 | R4 | R5 | MS (APcI +ve) $[M+H]^+$ (observed) | For Procedure see Example No. |
|---|---|---|---|---|---|---|---|---|
| 9 | A | Ph | H | 3-BrPh | H | H | 358/360 | 2 |
| 10 | A | Ph | H | 4-PhPh | H | H | 356 | 2 |
| 11 | A | Ph | H | 4-CF3Ph | H | H | 348 | 2 |
| 12 | A | Ph | H | 3-NO2Ph | H | H | 325 | 2 |
| 13 | A | Ph | H | 3-PhCOPh | H | H | 384 | 2 |
| 14 | A | Ph | H | 4-PhPhCH2 | H | H | 370 | 2 |
| 15 | A | Ph | H | 2-ThienylCH2 | H | H | 300 | 2 |
| 16 | A | 3-ClPh | H | PhSCH2 | H | H | 360/362 | 2 |
| 17 | A | 3-ClPh | H | 2-NaphthylCH2 | H | H | 378/380 | 2 |
| 18 | A | Ph | H | 3-PhOPh | H | H | 372 | 2 |
| 19 | A | 3-ClPh | H | Ph | H | H | 314/316 | 2 |
| 20 | A | Ph | H | Cyclohexyl | H | H | 286 | 2 |
| 21 | A | Ph | H | PhCH2 | H | H | 294 | 2 |
| 22 | A | Ph | H | 3-Pyridyl | H | H | 281 | 2 |
| 23 | A | Ph | H | 3,5-diClPh | H | H | 348/350/352 | 2 |
| 24 | A | Ph | H | 4-MeCOPh | H | H | 322 | 2 |
| 25 | A | Ph | H | 4-NO2Ph | H | H | 325 | 2 |
| 26 | A | Ph | H | 3-IndolylCH2 | H | H | 333 | 2 |
| 27 | A | Ph | H | 4-FPhCH2 | H | H | 312 | 2 |
| 28 | A | 3-ClPh | H | PhCO(CH2)2 | H | H | 370/372[a] | 2 |

| Example No. | Structure Type | R1 | R2 | R3 | R4 | R5 | MS (APcI +ve) $[M+H]^+$ (observed) | For Procedure see Example No. |
|---|---|---|---|---|---|---|---|---|
| 29 | A | Ph | H | Cyclopent-2-enylCH2 | H | H | 284 | 2 |
| 30 | A | 3-ClPh | H | Ph(CH2)3 | H | H | 356/358 | 2 |
| 31 | A | 3-ClPh | H | Ph2CHCH2 | H | H | 418/420 | 2 |
| 32 | A | Ph | H | 4-PhPhNH | H | H | 371 | 4 |
| 33 | A | Ph | H | 4-PhOPhNH | H | H | 387 | 4 |
| 34 | A | Ph | H | 4-Br-2-MePhNH | H | H | 387/389 | 4 |
| 35 | A | Ph | H | 1-NaphthylNH | H | H | 345 | 4 |
| 36 | A | Ph | H | 3-NO2PhNH | H | H | 340 | 4 |
| 37 | A | Ph | H | 3-MeOPhNH | H | H | 325 | 4 |
| 38 | A/B | H | H | Ph | H | H | 204 | 2 |
| 39 | A | 4-MeOPh | H | 4-ClPhNH | H | H | 359/361 | - |

a Mass spectrum obtained in ES +ve mode.

## Claims

1. A pharmaceutical composition, which composition comprises a compound of formula (I)




(I)

or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier wherein;

the $R^3CZ$- moiety may be attached to the nitrogen atom at position 1 or the nitrogen atom at position 2;

$R^1$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic;

$R^2$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic, or $R^1$ and $R^2$ together with the nitrogen atom to which they are attached may form a heterocyclic ring which ring may be unsubstituted or substituted;

$R^3$ is alkyl, aryl, aralkyl, aryl(Q)alkyl, where Q is O or S, aralkenyl, alicyclic, heteroaryl, heteroaralkyl, arylcarbonylalkyl, alicyclylalkyl, diarylalkyl, or $NR^6R^7$;

$R^4$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic;

$R^5$ is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic, or $R^4$ and $R^5$ together with the nitrogen atom to which they are attached may form a heterocyclic ring which ring may be unsubstituted or substituted;

$R^6$ is hydrogen, aryl or alicyclic;

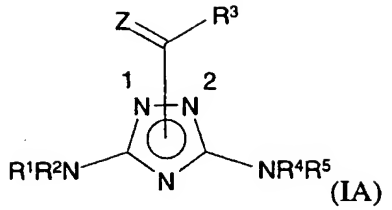
$R^7$ is hydrogen, aryl or alicyclic, and;

Z is oxygen or sulphur.

2. A pharmaceutical composition according to claim 1 wherein the compound of formula (I) is selected from the list consisting of:
3-amino-5-anilino-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-*trans*-(2-furyl)acryloyl)1,2,4,-triazole;
3-amino-5-anilino-1-(3-*trans*-(2-furyl)acryloyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide;
3-amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide;
3-amino-5-(5-chloro-2-methylanilino)-2-benzoyl-1,2,4-triazole;

3-amino-5-anilino-2-(4-chlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-naphthoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-phenylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-trifluoromethylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-((3-benzoyl)benzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-biphenylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-thienylacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-phenylthioacetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(2-naphthylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-phenoxybenzoyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-cyclohexylcarbonyl-1,2,4-triazole;
3-amino-5-anilino-2-phenylacetyl-1,2,4-triazole;
3-amino-5-anilino-2-(3-nicotinoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3,5-dichlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-acetylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-indolylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-fluorophenylacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3-benzoylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(cyclopent-2-enyl)acetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(4-phenylbutyroyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3,3-diphenylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid 4-biphenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-phenoxyphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-bromo-2-methylphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (1-naphthyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-nitrophenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-methoxyphenyl)amide;
3,5-diamino-2-benzoyl-1,2,4-triazole, and;
3-amino-5-(4-methoxyanilino)-1,2,4-triazole-2-carboxylic acid (4-chlorophenyl)amide;
or a pharmaceutically acceptable derivative thereof.

3. A compound of formula (IA) or a derivative thereof



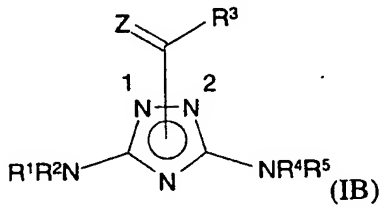

(IA)

wherein
$R^1$, $R^2$, $R^3$, $R^4$, $R^5$, and Z are as defined in relation to formula (I) of claim 1, with the proviso that the compounds of formula (IA) do not include:
3,5-diamino-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-acetyl-1,2,4-triazole, and;
3-amino-5-(4-methoxyanilino)-1,2,4-triazole-2-carboxylic acid (4-chlorophenyl)amide.

4. A compound of formula (IA) or a derivative thereof according to claim 3 selected from the list consisting of:
3-amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-*trans*-(2-furyl)acryloyl)-1,2,4,-triazole;
3-amino-5-anilino-1-(3-*trans*-(2-furyl)acryloyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide;
3-amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide;
3-amino-5-(5-chloro-2-methylanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-(4-chlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-naphthoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-phenylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-trifluoromethylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-((3-benzoyl)benzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-biphenylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-thienylacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-phenylthioacetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(2-naphthylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-phenoxybenzoyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-cyclohexylcarbonyl-1,2,4-triazole;
3-amino-5-anilino-2-phenylacetyl-1,2,4-triazole;
3-amino-5-anilino-2-(3-nicotinoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3,5-dichlorobenzoyl)-1,2,4-triazole;

3-amino-5-anilino-2-(4-acetylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-indolylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-fluorophentlacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3-benzoylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(cyclopent-2-enyl)acetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(4-phenylbutyroyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3,3-diphenylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid 4-biphenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-phenoxyphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-bromo-2-methylphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (1-naphthyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-nitrophenyl)amide, and;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-methoxyphenyl)amide.

5. A compound of formula (IB) or a derivative thereof



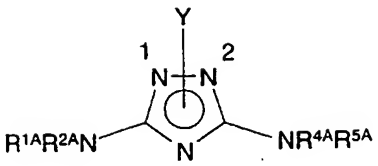
(IB)

wherein
$R^1$, $R^2$, $R^3$, $R^4$, $R^5$, and Z are as defined in relation to formula (I) of claim 1, with the proviso that the compounds of formula (IB) do not include:
3,5-diamino-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-benzoyl-1,2,4-triazole, and;
3-amino-5-(4-methoxyanilino)-1,2,4-triazole-2-carboxylic acid (4-chlorophenyl)amide.

6. A compound of formula (IB) according to claim 5 or a derivative thereof selected from the list consisting of:
3-amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-*trans*-(2-furyl)acryloyl)-1,2,4,-triazole;
3-amino-5-anilino-1-(3-*trans*-(2-furyl)acryloyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide;
3-amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide;

3-amino-5-(5-chloro-2-methylanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-(4-chlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-naphthoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-phenylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-trifluoromethylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-((3-benzoyl)benzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-biphenylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(2-thienylacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-phenylthioacetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(2-naphthylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-phenoxybenzoyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-benzoyl-1,2,4-triazole;
3-amino-5-anilino-2-cyclohexylcarbonyl-1,2,4-triazole;
3-amino-5-anilino-2-phenylacetyl-1,2,4-triazole;
3-amino-5-anilino-2-(3-nicotinoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3,5-dichlorobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-acetylbenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-nitrobenzoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(3-indolylacetyl)-1,2,4-triazole;
3-amino-5-anilino-2-(4-fluorophenylacetyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3-benzoylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-2-(cyclopent-2-enyl)acetyl-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(4-phenylbutyroyl)-1,2,4-triazole;
3-amino-5-(3-chloroanilino)-2-(3,3-diphenylpropanoyl)-1,2,4-triazole;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid 4-biphenylamide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-phenoxyphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-bromo-2-methylphenyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (1-naphthyl)amide;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-nitrophenyl)amide, and;
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-methoxyphenyl)amide.

7. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein Z is O and $R^3$ is other than $NR^6R^7$, or a derivative thereof, which process comprises the reaction of a compound of formula (II)



(II)

wherein Y is hydrogen and $R^{1A}$, $R^{2A}$, $R^{4A}$ and $R^{5A}$ are respectively $R^1$, $R^2$, $R^4$ and $R^5$ as hereinbefore defined or a protected form thereof, with a compound of formula (III)

$R^{3A}X$

(III)

wherein $R^{3A}$ is alkyl, aryl, aralkyl, aryl(Q)alkyl, where Q is O or S, aralkenyl, alicyclic, heteroaryl, heteroaralkyl, arylcarbonylalkyl, alicyclylalkyl, diarylalkyl, or a protected form thereof, and X is a suitable acylating group such as –COL, wherein L is a hydroxy group which has been activated by esterification with, for example, 1-hydroxybenzotriazole, or L is a suitable leaving group such as chloro, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I), wherein Z is O and $R^3$ is other than $NR^6R^7$, to a further compound of formula (I), wherein Z is O and $R^3$ is other than $NR^6R^7$;

(ii) removing any necessary protecting group;

(iii) preparing a derivative of the compound so formed.

8. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein Z is O and $R^3$ is $NHR^6$, or a derivative thereof, which process comprises the reaction of a compound of formula (II) as defined in claim 7 with a compound of formula (IV)

$R^{6A}T$

(IV)

wherein $R^{6A}$ is $R^6$ as hereinbefore defined, or a protected form thereof, and T is a suitable aminocarbonylating group such as isocyanate, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I), wherein Z is O and $R^3$ is $NHR^6$, to a further compound of formula (I), wherein Z is O and $R^3$ is $NHR^6$;

(ii) removing any necessary protecting group;

(iii) preparing a derivative of the compound so formed.

9. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein Z is S and $R^3$ is other than $NR^6R^7$, or a derivative thereof, which process comprises the reaction of a compound of formula (II) as defined in claim 7 with a compound of formula (V)

$R^{3A}W$

(V)

wherein $R^{3A}$ is alkyl, aryl, aralkyl, aryl(Q)alkyl, where Q is O or S, aralkenyl, alicyclic, heteroaryl, heteroaralkyl, arylcarbonylalkyl, alicyclylalkyl, diarylalkyl, or a protected form thereof, and W is a suitable thioacylating group such as –CSM, wherein M is a suitable leaving group such as chloro, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I), wherein Z is S and $R^3$ is other than $NR^6R^7$, to a further compound of formula (I), wherein Z is S and $R^3$ is other than $NR^6R^7$;

(ii) removing any necessary protecting group;

(iii) preparing a derivative of the compound so formed.

10. A process for the preparation of a compound of formula (I) as defined in claim 1, wherein Z is S and $R^3$ is $NHR^6$, or a derivative thereof, which process comprises the reaction of a compound of formula (II) as defined in claim 7 with a compound of formula (VI)

$R^{6A}U$

(VI)

wherein $R^{6A}$ is $R^6$ as hereinbefore defined, or a protected form thereof, and U is a suitable aminothiocarbonylating group such as isothiocyanate, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I), wherein Z is S and $R^3$ is $NHR^6$, to a further compound of formula (I), wherein Z is S and $R^3$ is $NHR^6$;

(ii) removing any necessary protecting group;

(iii) preparing a derivative of the compound so formed.

11. A compound of formula (I) as defined in claim 1, or a derivative thereof, for use in the treatment of conditions associated with the need for the

inhibition of GSK-3 such as diabetes, especially Type 2 diabetes, dementias such as Alzheimer's disease and manic depression.

12. Use of a compound of formula (I) as defined in claim 1, or a derivative thereof, for the manufacture of a medicament for the treatment of conditions associated with the need for the inhibition of GSK-3 such as diabetes, especially Type 2 diabetes, dementias such as Alzheimer's disease and manic depression.

13. A method for the treatment of conditions associated with the need for the inhibition of GSK-3 such as diabetes, especially Type 2 diabetes, dementias such as Alzheimer's disease and manic depression, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I) as defined in claim 1 or a derivative thereof.

# INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 00/07423

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D249/14 C07D405/06 C07D401/06 A61K31/4196 A61P7/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 2 352 944 A (GENERAL ELECTRIC CO.)<br>4 July 1944 (1944-07-04)<br>the whole document | 1-13 |
| A | EP 0 162 217 A (CIBA GEIGY AG)<br>27 November 1985 (1985-11-27)<br>claims | 1-13 |
| P,A | WO 00 10563 A (SMITHKLINE BEECHAM CORP<br>;ADAMS JERRY L (US); LEE DENNIS (US))<br>2 March 2000 (2000-03-02)<br>claims | 1-13 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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| 12 December 2000 | 19/12/2000 |

| Name and mailing address of the ISA | Authorized officer |
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# INTERNATIONAL SEARCH REPORT

..:formation on patent family members

Inte: ɔnal Application No
PCT/EP 00/07423

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alkylphosphonate or mono- or bis-alkylphosphonate$C_{1-6}$alkyl, hydroxamic acids or esters thereof, or any two adjacent substituents on the phenyl ring together with the carbon atoms to which they are attached form a carbocyclic ring or a heterocyclic ring.

The terms "heterocyclyl" and "heterocyclic" when used herein suitably include, unless otherwise defined, aromatic and non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur, which rings, may be unsubstituted or substituted by, for example, up to three substituents. Each ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring.

Substituents for any heterocyclyl or heterocyclic group are suitably selected from halogen, alkyl, arylalkyl, alkoxy, alkoxyalkyl, haloalkyl, hydroxy, amino, mono- and di-N-alkyl-amino, acylamino, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-alkylcarbonyl, aryloxycarbonyl, alkoxycarbonylalkyl, aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, alkylthio, alkylsulphinyl, alkylsulphonyl, heterocyclyl, heterocyclylalkyl, and hydroxamic acids or esters thereof.

When used herein 'halo' includes iodo, bromo, chloro or fluoro, especially chloro or fluoro.

Suitable derivatives of the compounds of the invention are pharmaceutically acceptable derivatives.

Suitable derivatives of the compounds of the invention include salts and solvates.

Suitable pharmaceutically acceptable derivatives include pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-b-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable pharmaceutically acceptable salts also includes pharmaceutically acceptable acid addition salts, such as those provided by pharmaceutically acceptable inorganic acids or organic acids.